ORIGINAL ARTICLE

High-Flow or Standard Oxygen in Acute Hypoxemic Respiratory Failure

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ABSTRACT

BACKGROUND

Data are needed on the effect of oxygen delivered through a high-flow nasal cannula, as compared with standard oxygen therapy, on intubation and mortality in patients with acute hypoxemic respiratory failure.

METHODS

In this multicenter, open-label trial, we randomly assigned patients who had acute hypoxemic respiratory failure to receive high-flow-oxygen or standard-oxygen therapy. All the patients had a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 or less, a respiratory rate of more than 25 breaths per minute, and pulmonary infiltrate on chest imaging. The primary outcome was death by day 28.

RESULTS

A total of 1116 patients underwent randomization. Of these patients, 1110 (556 in the high-flow-oxygen group and 554 in the standard-oxygen group) were included in the analysis. Mortality at day 28 was 14.6% (in 81 of 556 patients) in the high-flow-oxygen group and 14.6% (in 81 of 554 patients) in the standard-oxygen group (difference, −0.05 percentage points; 95% confidence interval [CI], −4.21 to 4.10; P=0.98). The incidence of intubation by day 28 was 42.4% (in 236 of 556 patients) in the high-flow-oxygen group and 48.4% (in 268 of 554 patients) in the standard-oxygen group (difference, −5.93 percentage points; 95% CI, −11.78 to −0.08). Serious adverse events (cardiac arrest or pneumothorax) occurred during spontaneous breathing in 13 patients (2.3%) in the high-flow-oxygen group and in 6 patients (1.1%) in the standard-oxygen group.

CONCLUSIONS

Among patients with acute hypoxemic respiratory failure, the use of oxygen delivered through a high-flow nasal cannula did not significantly reduce mortality at day 28. (Funded by the French Ministry of Health and Fisher and Paykel Healthcare; SOHO ClinicalTrials.gov number, NCT04468126.)

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*A complete list of investigators in the SOHO Trial Group and the REVA Network is provided in the Supplementary Appendix, available at NEJM.org.

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Acute respiratory failure is the leading cause of admission to intensive care units (ICUs), accounting for approximately three quarters of admissions worldwide.[1] Acute hypoxemic respiratory failure in the absence of cardiogenic pulmonary edema or chronic respiratory diseases is caused primarily by viral or bacterial pneumonia and is associated with the worst outcomes.[2,3]

The administration of oxygen is the first-line therapy and can be given with a standard nonrebreather mask, with high-flow oxygen through nasal cannula, or with noninvasive ventilation through a face mask. The primary goal is to avoid endotracheal intubation, because invasive mechanical ventilation is associated with severe adverse events and can result in high mortality.[2,4]

Although standard oxygen is the most common approach to treating patients with acute hypoxemic respiratory failure, such therapy is limited in its ability to provide high levels of fraction of inspired oxygen (FIO_2) and to unload inspiratory effort.[3,5] In contrast, high-flow oxygen and noninvasive ventilation improve oxygenation and relieve patient effort and dyspnea.[6-8] In 2015, investigators in a seminal trial found better survival with high-flow oxygen than with standard oxygen and noninvasive ventilation.[3,9] This decreased mortality was driven by a decreased use of intubation in the patients with the most severe disease.[3] Several trials that were conducted during the coronavirus disease 2019 (Covid-19) pandemic suggested a beneficial effect of high-flow-oxygen therapy regarding the risk of intubation.[10-12] Current guidelines recommend the use of high-flow oxygen rather than noninvasive ventilation and standard oxygen as first-line therapy for acute hypoxemic respiratory failure with respect to a reduced risk of intubation, although results regarding mortality are less consistent.[13,14]

To address the lack of evidence on whether high-flow oxygen is superior to standard oxygen in reducing mortality and to assess its beneficial effects on intubation, we conducted a multicenter clinical trial to compare these two oxygenation strategies in patients who were admitted to an ICU for acute hypoxemic respiratory failure. The primary objective was to assess mortality at day 28 with high-flow oxygen as compared with standard oxygen.

Methods

Trial Design and Oversight

The SOHO (Standard Oxygen versus High-Flow Oxygen Therapy in Acute Hypoxemic Respiratory Failure) trial was an investigator-initiated, multicenter, open-label, randomized clinical trial conducted in 42 ICUs in France. The trial protocol (available with the full text of this article at NEJM.org) was approved by the central ethics committee at each trial center and has been published previously.[15] In accordance with the French regulatory guidelines, no safety monitoring committee was required. Consent from patients or agreement from their family or another surrogate was obtained orally before enrollment in the trial, with a written record maintained by the investigator.

The trial was funded by the French Ministry of Health and by a grant from Fisher and Paykel Healthcare. The trial was designed and overseen by the steering committee. All the investigators vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Data collection was regularly monitored by research assistants. The trial statisticians and the steering committee vouch for the data and analyses. The first author drafted the manuscript, and all the authors critically reviewed, revised, and approved the final version for submission for publication. The trial funders and the trial-coordination sponsor (University Hospital, Poitiers, France) were not involved in the trial design, data analysis or interpretation, or writing of the manuscript.

After the onset of the Covid-19 pandemic, a substudy (called SOHO-COVID) was approved in April 2021 by the central ethics committee and conducted through December 2021.[11,15] This substudy exclusively enrolled patients with respiratory failure related to Covid-19. To maximize the robustness and timeliness of the findings of the current report, we integrated data from the 324 patients with Covid-19–related respiratory failure who had been enrolled in the SOHO trial between January and April 2021. None of the data for patients who were enrolled later in the SOHO-COVID trial[11,15] are included in the current report.

Trial Population

Consecutive adult patients (≥18 years of age) who had been admitted to an ICU with acute hypox-

emic respiratory failure were eligible if they met all the following criteria: a respiratory rate of more than 25 breaths per minute, pulmonary infiltrates on chest imaging, and a ratio of partial pressure of arterial oxygen (PaO_2; measured in mm Hg) to the fraction of inspired oxygen (FIO_2) of 200 or less while breathing oxygen at a flow of 10 liters per minute or more through a nonrebreather mask. For the calculation of the PaO_2:FIO_2 ratio, the FIO_2 was estimated as 0.03 × (oxygen flow in liters/min) + 0.21.[3,16]

The main exclusion criteria were a partial pressure of arterial carbon dioxide ($PaCO_2$) of more than 45 mm Hg, exacerbation of chronic obstructive pulmonary disease or another chronic lung disease with long-term oxygen or ventilatory support, cardiogenic pulmonary edema, hemodynamic instability with signs of hypoperfusion or use of vasopressors at more than 0.3 μg per kilogram of body weight per minute, an altered consciousness (as defined by a score of <12 points on the Glasgow Coma Scale), respiratory failure within 7 days after extubation or abdominal or cardiothoracic surgery, need for emergency intubation, or a do-not-intubate order. Covid-19–related respiratory failure was secondarily added as an exclusion criterion after the publication of the SOHO-COVID substudy, which showed a decreased incidence of intubation in patients who were treated with high-flow oxygen.[11] Details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

Randomization was performed in permuted blocks of four (unknown to investigators), with stratification according to immunosuppression status. (Details are provided in the Supplementary Appendix.)[17-19] Within the first 3 hours after validation of inclusion criteria, patients were randomly assigned in a 1:1 ratio by a centralized Web-based system to the high-flow-oxygen group or to the standard-oxygen group.

INTERVENTIONS

In the high-flow-oxygen group, oxygen was delivered through a heated humidifier (MR850, Fisher and Paykel Healthcare) and was applied continuously through large-bore binasal prongs, with a gas flow rate of at least 50 liters per minute. The FIO_2 was adjusted to maintain oxygen saturation, as measured by a pulse-oximetry level of 92 to 96% (Optiflow or Airvo-2, Fisher and Paykel Healthcare; or by a dedicated ICU ventilator with the option of high-flow-oxygen therapy). High-flow oxygen was provided for at least 48 hours. After 48 hours of treatment, high-flow oxygen could be stopped and switched to standard oxygen if the patient had a respiratory rate of less than 25 breaths per minute and a pulse-oximetry level of at least 92% with a FIO_2 of 40% or less.[20] In case of the above-mentioned signs of persistence of respiratory failure, treatment was continued until respiratory recovery or intubation.

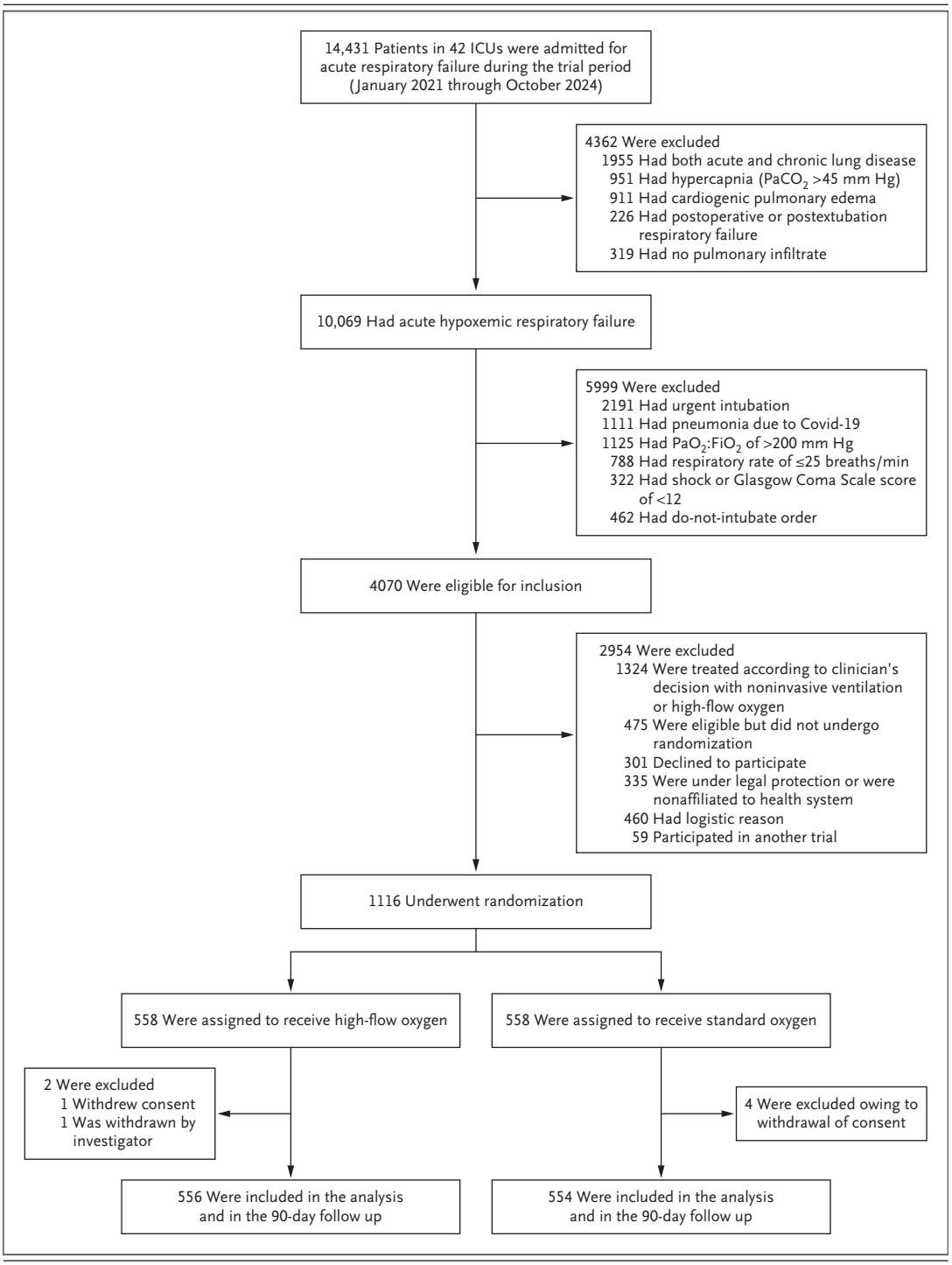
In the standard-oxygen group, oxygen was continuously delivered through a nonrebreather mask, with oxygen flow set at 10 liters per minute or more, adjusted to maintain a pulse-oximetry level ranging from 92 to 96% until recovery or intubation. (Details regarding the interventions are provided in the Supplementary Appendix.)

OUTCOMES

The primary outcome was death from any cause 28 days after randomization. Key secondary outcomes were endotracheal intubation within 28 days after randomization, the interval between randomization and intubation, the number of ventilator-free days (i.e., days alive without invasive mechanical ventilation) between randomization and day 28, death at various prespecified times (in the ICU, in the hospital, and until day 90), and the lengths of ICU and hospital stays.

Other prespecified outcomes included the following respiratory measures obtained 1 hour and 6 hours after treatment initiation: level of oxygenation, respiratory rate, dyspnea score on a 100-mm visual analogue scale (with higher scores indicating more severe dyspnea), and grade of patient-perceived dyspnea on the 5-point Likert scale (slight or marked alleviation of dyspnea, no change, or slight or marked worsening). Data regarding the overall incidence of serious adverse events were also obtained.

To ensure the consistency of intubation indications across participating centers and reduce the risk of delayed intubation, the following prespecified criteria for endotracheal intubation were applied: severe respiratory failure, recurrent epi-


14,431 Patients in 42 ICUs were admitted for acute respiratory failure during the trial period (January 2021 through October 2024)
4362 Were excluded
1955 Had both acute and chronic lung disease
951 Had hypercapnia ($PaCO_2$ >45 mm Hg)
911 Had cardiogenic pulmonary edema
226 Had postoperative or postextubation respiratory failure
319 Had no pulmonary infiltrate
10,069 Had acute hypoxemic respiratory failure
5999 Were excluded
2191 Had urgent intubation
1111 Had pneumonia due to Covid-19
1125 Had PaO_2:FiO_2 of >200 mm Hg
788 Had respiratory rate of ≤25 breaths/min
322 Had shock or Glasgow Coma Scale score of <12
462 Had do-not-intubate order
4070 Were eligible for inclusion
2954 Were excluded
1324 Were treated according to clinician's decision with noninvasive ventilation or high-flow oxygen
475 Were eligible but did not undergo randomization
301 Declined to participate
335 Were under legal protection or were nonaffiliated to health system
460 Had logistic reason
59 Participated in another trial
1116 Underwent randomization
558 Were assigned to receive high-flow oxygen
558 Were assigned to receive standard oxygen
2 Were excluded
1 Withdrew consent
1 Was withdrawn by investigator
4 Were excluded owing to withdrawal of consent
556 Were included in the analysis and in the 90-day follow up
554 Were included in the analysis and in the 90-day follow up

sodes of a pulse-oximetry level of less than 80% or a persistent level of less than 88% with maximal oxygen support, cardiac arrest, hemodynamic instability with signs of hypoperfusion, or deterioration of neurologic status. Severe respiratory failure leading to intubation was defined by at least two of the following criteria: a respiratory rate of more than 40 breaths per minute, appearance or worsening of signs of respiratory-muscle fatigue, acidosis with a pH of less than 7.35, or one or more of the following three factors: a pulse-oximetry level of less than 92%, a

Figure 1 (facing page). Enrollment, Randomization, Intervention, and Follow-up.

Shown are enrollment data for patients with acute hypoxemic respiratory failure who were assigned to receive either high-flow-oxygen therapy or standard-oxygen therapy. Patients may have had more than one reason for exclusion from the trial. Those who are described as being under legal protection were minors, persons deprived of liberty by a judicial or administrative decision, or adults under any other legal protection. One patient was withdrawn by the investigator immediately after randomization because of an urgent need for intubation, which constituted an exclusion criterion. No treatment was administered to that patient, and no data regarding either primary or secondary outcomes were collected. In September 2022, pneumonia caused by coronavirus disease 2019 (Covid-19) was added as an exclusion criterion. FIO_2 denotes fraction of inspired oxygen, ICU intensive care unit, $PaCO_2$ partial pressure of arterial carbon dioxide, and PaO_2 partial pressure of arterial oxygen.

PaO_2:FIO_2 ratio of less than 100 mm Hg despite oxygen flow of at least 15 liters per minute, or an FIO_2 level of 80% or more. (See the Supplementary Appendix for additional details.)

STATISTICAL ANALYSIS

We calculated that a sample size of 1110 patients would provide the trial with 80% power to show an absolute between-group difference of 6 percentage points in mortality at day 28 (i.e., 12% in the high-flow-oxygen group and 18% in the standard oxygen group), at a two-sided alpha level of 0.05.[3,21]

All the analyses were performed by the trial statisticians according to a prespecified statistical analysis plan (modified as requested by the statistical editor at the *Journal*), which is provided with the protocol. The analyses were performed on an intention-to-treat basis after protocol deviations had been assessed by a review committee whose members were unaware of trial-group assignments.

We used a chi-square test to compare the numbers of deaths in the two groups at day 28 (primary outcome). The treatment effect was reported as absolute differences and 95% confidence intervals on the basis of the simple-contrasts method. Adjustment for the stratification variable and the center effect was performed with a binomial generalized-estimating-equation model with an identity link, from which adjusted risk differences and 95% confidence intervals were derived. Kaplan–Meier curves were plotted to assess the time from randomization to death at day 28.

Effect estimates for secondary outcomes were reported as the absolute difference for qualitative variables and as the mean or median difference for quantitative variables with 95% confidence intervals. We used unstratified bootstrapping (10,000 samples with replacement) to calculate the median difference. Confidence intervals for secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing. The cumulative incidence of intubation from randomization to day 28 was estimated with the Aalen–Johansen method, with the treatment of death without previous intubation as a competing event.

Prespecified subgroup analyses were performed in immunocompromised patients and in those with severe hypoxemia at baseline (PaO_2:FIO_2 ratio of ≤100 mm Hg). Post hoc analyses were performed in patients with Covid-19.

Missing data were addressed through multiple imputation by chained equations under a missing-at-random assumption. The imputation model included the following variables: predictors of missingness, treatment assignment, and stratification factor. Rubin's rules were then applied to estimate the difference and 95% confidence intervals across the imputed datasets. A two-sided P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with R software, version 4.0.4 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

From January 2021 through October 2024, a total of 4070 patients with acute hypoxemic respiratory failure who had been admitted to the 42 participating ICUs were eligible for inclusion; of these patients, 1116 underwent randomization. After the exclusion of 6 patients (5 who had withdrawn consent and 1 who was withdrawn by the investigator), 1110 patients were included in the intention-to-treat analysis: 556 patients in the high-flow-oxygen group and 554 in the standard-oxygen group (Fig. 1). Of the 324 patients whose results were previously reported in the SOHO-COVID substudy,[11] 164 were included in the high-

flow-oxygen group and 160 were included in the standard-oxygen group.

The baseline characteristics of the patients appeared to be well balanced between the groups, except that the high-flow-oxygen group had a higher percentage of men, a higher median dyspnea score, and a lower respiratory rate than the standard-oxygen group (Table 1). The baseline characteristics of the patients after the exclusion of those who were also included in the SOHO-COVID substudy are shown in Table S1 in the Supplementary Appendix. These data suggest that the population was representative of patients with acute hypoxemic respiratory failure in a high-income country (Table S2).

The percentage of patients with immunocompromise was 22.3% (248 of 1110 patients). Pneumonia was the primary cause of respiratory failure in 978 patients (88.1%), including 592 cases of viral pneumonia (53.3%), of which 517 were attributable to Covid-19, and 352 cases of bacterial pneumonia (31.7%) (Table S3). The mean respira-

Table 1. Characteristics of the Patients at Baseline.*

Variables	High-Flow Oxygen (N=556)	Standard Oxygen (N=554)
Age — yr	62±13	63±13
Male sex — no. (%)	411 (73.9)	364 (65.7)
Body-mass index†	28±6	28±6
SAPS II‡	35±13	34±14
Median SOFA score (IQR)§	2 (2–3)	2 (2–3)
Median Clinical Frailty Score (IQR)¶	2 (1–3)	2 (1–3)
Current smoker — no. (%)	72 (12.9)	90 (16.2)
Coexisting illness — no. (%)		
Immunosuppression‖	124 (22.3)	124 (22.4)
Ischemic heart disease	52 (9.4)	53 (9.6)
Chronic lung disease	61 (11.0)	61 (11.0)
Main reason for acute respiratory failure — no. (%)		
Viral pneumonia	300 (54.0)	292 (52.7)
Covid-19	258 (46.4)	259 (46.8)
Bacterial pneumonia	172 (30.9)	180 (32.5)
Fungal pneumonia	17 (3.1)	17 (3.1)
Other reason	67 (12.1)	65 (11.7)
Medication — no. (%)		
Glucocorticoid	343 (62.3)	338 (62.0)
Vasopressor	13 (2.3)	8 (1.4)
Bilateral pulmonary infiltrates — no. (%)	491 (88.3)	478 (86.3)
Clinical measure		
Heart rate — beats/min	92±21	92±22
Respiratory rate — breaths/min	30±5	31±6
Median dyspnea score (IQR) — mm**	33 (9–59)	25 (5–50)
Oxygen flow rate — liters/min	13±3	13±3
Arterial blood gas		
pH	7.45±0.05	7.45±0.06
Pao_2 — mm Hg	76±17	76±16
Pao_2:Fio_2 ratio††	131±32	132±32
$Paco_2$ — mm Hg	35±5	35±5

Table 1. (Continued.)

Variables	High-Flow Oxygen (N=556)	Standard Oxygen (N=554)
Arterial pressure — mm Hg		
Systolic	129±22	129±22
Mean	90±15	90±15
Median time between ICU admission and randomization (IQR) — hr	2.5 (1.3–5.9)	2.4 (1.4–6.4)

* Plus–minus values are means ±SD. French law prohibits the collection of information regarding race or ethnic group. Covid-19 denotes coronavirus 2019 disease, F_{IO_2} fraction of inspired oxygen, ICU intensive care unit, IQR interquartile range, P_{aCO_2} partial pressure of arterial carbon dioxide, and P_{aO_2} partial pressure of arterial oxygen.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The Simplified Acute Physiology Score (SAPS) II was calculated on the basis of 15 variables, information about previous health status, and information obtained at admission. Scores range from 0 to 163, with higher scores indicating more severe disease.
§ The Sequential Organ Failure Assessment (SOFA) score was obtained on the day of initial spontaneous breathing. Scores range from 0 to 24, with higher scores indicating more severe organ failure.
¶ The Clinical Frailty Score is a summary of the overall level of fitness or frailty after clinical evaluation. Scores range from 1 to 9, with higher scores indicating greater frailty.
‖ Immunosuppression was defined as use of long-term (>3 months) or high-dose glucocorticoids (20 mg per day of prednisone or its equivalent for ≥14 days), use of other immunosuppressant or immunomodulatory drugs, solid organ transplantation, active solid cancer, hematologic cancer (active or in remission for <5 years), leukopenia (white-cell count, $<1.0\times10^9$ per liter) or neutropenia (neutrophil count, $<0.5\times10^9$ per liter) after chemotherapy, allogeneic stem-cell transplantation within the previous 5 years, acquired immunodeficiency syndrome, or primary immune deficiency.
** The dyspnea score was measured on a 100-mm visual analogue scale. Scores range from 0 to 100 mm, with higher scores indicating greater dyspnea.
†† For the calculation of the P_{aO_2}:F_{IO_2} ratio in the standard-oxygen group, the P_{aO_2} was measured in mm Hg and the F_{IO_2} was estimated as 0.03 × (oxygen flow in liters/min) + 0.21. In the high-flow-oxygen group, the F_{IO_2} was set directly on the air–oxygen blender.

tory rate at baseline was 31±6 breaths per minute, the P_{aO_2}:F_{IO_2} ratio was 132±32 mm Hg, and 193 patients (17%) had a P_{aO_2}:F_{IO_2} ratio of 100 mm Hg or less.

INTERVENTIONS

The initial mean settings were as follows: gas flow of 51±9 liters per minute and F_{IO_2} of 0.67±0.17 in the high-flow-oxygen group and oxygen flow of 12±3 liters per minute in the standard-oxygen group. High-flow oxygen was initiated within a median time of 18 minutes (interquartile range, 6 to 35) after randomization. Both high-flow oxygen and standard oxygen were continuously delivered for a median time of 4 days (interquartile range, 3 to 6) in patients who did not undergo intubation. Treatment was discontinued because of discomfort with the oxygen device in 44 patients (4.3%), including 30 patients who were initially assigned to receive high-flow oxygen and were switched to standard oxygen and 14 patients who were initially assigned to receive standard oxygen and were switched to high-flow oxygen (Table S4). Noninvasive ventilation was applied as rescue therapy in 37 patients (3.3%): 15 patients in the high-flow-oxygen group and 22 patients in the standard-oxygen group.

PRIMARY AND SECONDARY OUTCOMES

The mortality at day 28 was 14.6% (81 of 556 patients) in the high-flow-oxygen group and 14.6% (81 of 554 patients) in the standard-oxygen group (absolute difference, −0.05 percentage points; 95% confidence interval [CI], −4.2 to 4.1; P=0.98) (Table 2, Fig. 2, and Fig. S1). The incidence of intubation at day 28 was 42.4% (236 of 556 patients) in the high-flow-oxygen group and 48.4% (268 of 554) in the standard-oxygen group (absolute difference, –5.93 percentage points; 95% CI, –11.78 to –0.08) (Table 2 and Fig. 2).

The median time from randomization until intubation was 24 hours (interquartile range, 10 to 67) with high-flow oxygen and 23 hours (interquartile range, 10 to 47) with standard oxygen (absolute difference, 0.4 hours; 95% CI, −6.8 to 6.5) (Table 2). The median number of ventilator-free days at day 28 was 28 (interquartile range, 11 to 28) in the high-flow-oxygen group and 26

Table 2. Primary and Secondary Outcomes.*

Outcome	High-Flow Oxygen (N=556)	Standard Oxygen (N=554)	Difference (95% CI)†	P Value
Primary outcome				
Death by day 28 — no. (%)				
Unadjusted analysis	81 (14.6)	81 (14.6)	−0.05 (−4.21 to 4.10)	0.98
Adjusted analysis‡	81 (14.6)	81 (14.6)	−0.28 (−3.88 to 3.33)	—
Secondary outcomes				
Intubation at day 28 — no. (%)	236 (42.4)	268 (48.4)	−5.93 (−11.78 to −0.08)	—
Median time from randomization to intubation (IQR) — hr	24 (10 to 67)	23 (10 to 47)	0.4 (−6.8 to 6.5)	—
Median ventilator-free time at day 28 (IQR) — days§	28 (11 to 28)	26 (10 to 28)	2.0 (0.0 to 4.0)	—
Death — no. (%)				
In ICU	81 (14.6)	82 (14.8)	−0.2 (−4.4 to 3.9)	—
In hospital	94 (16.9)	99 (17.9)	−1.0 (−5.4 to 3.5)	—
By day 90	98 (17.6)	104 (18.8)	−1.2 (−5.7 to 3.4)	—
Median duration of invasive ventilation (IQR) — days	0 (0–9)	0 (0–10)	0.0 (−2.0 to 0.0)	
Median length of stay (IQR) — days				
In ICU	7 (4 to 13)	8 (4 to 15)	−1.0 (−1.0 to 1.0)	—
In hospital	15 (10 to 24)	16 (10 to 26)	−1.0 (−3.0 to 1.0)	—
Analyses performed 1 hr after treatment initiation				
Pao_2 — mm Hg	75±22	82±25	−7.0 (−10.1 to −3.9)	—
Pao_2:FIo_2 ratio	120±41	144±51	−24 (−30.0 to −18.0)	—
$Paco_2$ — mm Hg	34±5	36±5	−2.0 (−2.6 to −1.3)	—
Respiratory rate — breaths/min	26±7	29±7	−3.0 (−3.8 to −2.2)	—
Dyspnea score (IQR) — mm¶‖	25 (9 to 50)	20 (5 to 50)	4.5 (−1.5 to 10.5)	—
Improved grade of patient-perceived dyspnea — no. (%)‖**	275 (49.5)	192 (34.7)	14.9 (8.6 to 21.1)	—

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity.
‡ This analysis was adjusted for the stratification variable and the center effect by means of a binomial generalized-estimating-equation model with an identity link.
§ In the analysis of ventilator-free time at day 28, one point was given for each day from the first day of randomization to day 28 that patients were both alive and free of invasive mechanical ventilation; 17 patients were alive with 0 ventilator-free days (7 in the high-flow-oxygen group and 10 patients in the standard-oxygen group), and 162 patients died with no ventilator-free days (81 in each treatment group).
¶ Data regarding the dyspnea score were missing for 225 patients (107 patients in the high-flow-oxygen group and 118 patients in the standard–oxygen group).
‖ The missingness of dyspnea score at 1 hour and the missingness of improved grade of patient-perceived dyspnea were assessed and found to be inconsistent with a completely random mechanism. Multiple imputation by chained equations was used. Regarding the dyspnea score, the imputation model included age, current smoking status, baseline dyspnea, pH, heart rate, treatment group, and immunosuppression status. Twenty imputed datasets were generated by means of predictive mean matching. Regarding the improvement of patient-perceived dyspnea, the imputation model included age, glucocorticoid use, baseline dyspnea, pH, treatment group, and immunosuppression status. Twenty-five imputed datasets were generated by means of logistic regression.
** Data regarding the improved grade of patient-reported dyspnea were missing for 263 patients (128 patients in the high-flow-oxygen group and 135 patients in the standard-oxygen group). The grade of dyspnea was measured on a 5-point Likert scale model, which indicated marked improvement, slight improvement, no change, slight deterioration, or marked deterioration.

(interquartile range, 10 to 28) in the standard oxygen group (absolute difference, 2.0 days; 95% CI, 0.0 to 4.0).

One hour after treatment initiation, the mean (±SD) respiratory rate was 26±7 breaths per minute with high-flow oxygen and 29±7 breaths per minute with standard oxygen (absolute difference, −3.0 breaths per minute; 95% CI, −3.8 to

–2.2). The mean level of carbon dioxide was 34±5 mm Hg with high-flow oxygen and 36±5 mm Hg with standard oxygen (absolute difference, –2.0 mm Hg; 95% CI, –2.6 to –1.3). The dyspnea score that was recorded 1 hour after treatment initiation was 25 mm in the high-flow-oxygen group and 20 mm in the standard-oxygen group (absolute difference, 4.5 mm; 95% CI, –1.5 to 10.5). An improved grade of patient-perceived dyspnea was reported by 49.5% of the patients in the high-flow-oxygen group and by 34.6% of those in the standard-oxygen group (absolute difference, 14.9 percentage points; 95% CI, 8.6 to 21.1) (Table 2).

Sensitivity analyses that were performed according to the findings in complete case analyses showed similar results (Table S5). The prespecified and post hoc subgroup analyses of mortality and intubation at day 28 are shown in Figure S2.

SAFETY OUTCOMES

Data regarding adverse events and reasons for intubation are provided in Table 3 and Table S4. During spontaneous breathing, 14 patients had pneumothorax (10 in the high-flow-oxygen group and 4 in the standard-oxygen group), and 5 patients had cardiac arrest leading to intubation (3 in the high-flow-oxygen group and 2 in the standard-oxygen group).

DISCUSSION

In this multicenter, randomized, open-label trial involving 1110 patients with acute hypoxemic respiratory failure, the use of high-flow oxygen did not result in lower mortality than the use of standard oxygen. High-flow oxygen appeared to reduce the risk of intubation, although firm conclusions cannot be made.

The trial was powered to detect a quite large reduction in mortality. The lower-than-expected event rate, which was consistent with the findings in previous studies,[3,10,11,22] reduced the statistical power. However, addressing uncertainty about smaller effects would require a trial with several thousand patients, a factor that poses substantial logistic and ethical challenges. The frequent use of glucocorticoids in our trial may have contributed to decreased mortality, as has been shown in both viral (Covid-19)[23] and bacterial pneumonia,[24] as might have other numerous interventions during invasive ventilation.[25,26,27,28]

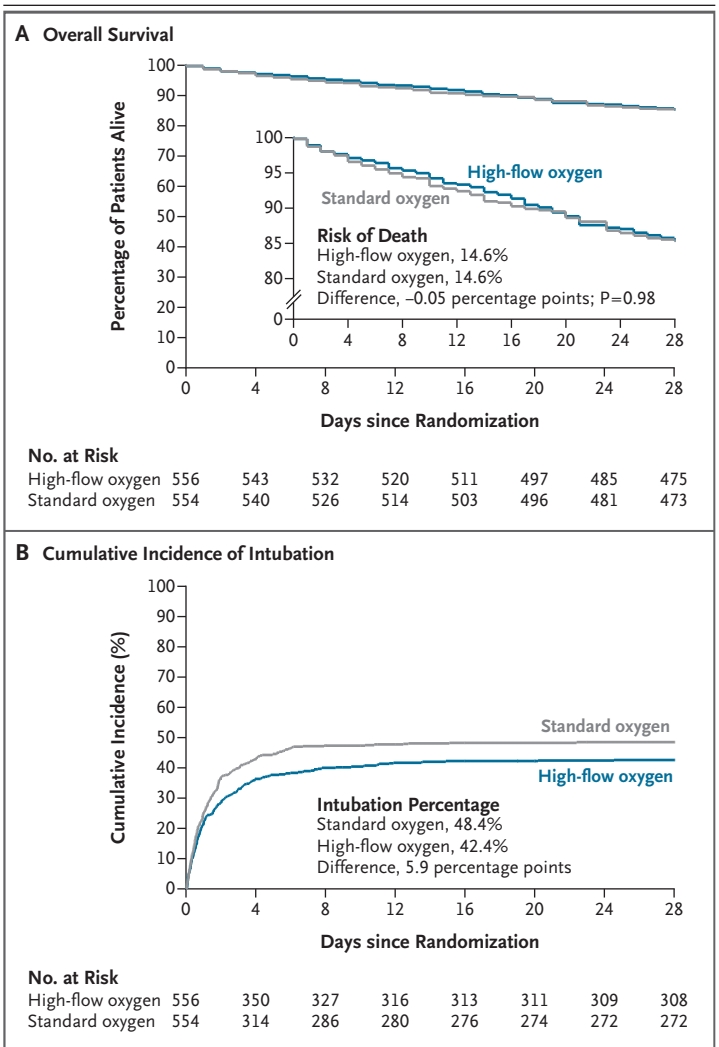

A Overall Survival
Percentage of Patients Alive
Days since Randomization
High-flow oxygen
Standard oxygen
Risk of Death
High-flow oxygen, 14.6%
Standard oxygen, 14.6%
Difference, –0.05 percentage points; P=0.98
No. at Risk
High-flow oxygen 556 543 532 520 511 497 485 475
Standard oxygen 554 540 526 514 503 496 481 473
B Cumulative Incidence of Intubation
Cumulative Incidence (%)
Days since Randomization
Standard oxygen
High-flow oxygen
Intubation Percentage
Standard oxygen, 48.4%
High-flow oxygen, 42.4%
Difference, 5.9 percentage points
No. at Risk
High-flow oxygen 556 350 327 316 313 311 309 308
Standard oxygen 554 314 286 280 276 274 272 272

Figure 2. Probability of Survival and Cumulative Incidence of Intubation.
Panel A shows the probability of survival during the first 28 days after randomization in the group that received high-flow oxygen and the group that received standard oxygen. The curves in the inset show the same data on an expanded y axis. Panel B shows the cumulative incidence of intubation during the first 28 days after randomization, with death considered as a competing event.

Clinicians should weigh uncertainty of effect on mortality against practical considerations — including patient comfort, risk of intubation, and local resources — when selecting oxygenation strategies.

High-flow oxygen appeared to reduce the incidence of intubation and to rapidly improve dyspnea, respiratory rate, and carbon dioxide values, as compared with standard oxygen, a finding that was consistent with its known physiological effects.[6,7] However, these potential benefits were

Table 3. Serious Adverse Events and Causes of Death.

Adverse Event or Cause of Death	High-Flow Oxygen (N=556)	Standard Oxygen (N=554)	P Value
Serious adverse events			
Serious adverse events during spontaneous breathing — no. (%)			
Cardiac arrest leading to intubation	3 (0.5)	2 (0.4)	1.00
Pneumothorax	10 (1.8)	4 (0.7)	0.11
Severe complications during intubation procedure — no./total no. (%)			
Cardiac arrest	4/236 (1.7)	4/268 (1.5)	1.00
Severe arterial hypotension*	26/236 (11.0)	24/268 (9.0)	0.44
Pulse-oximetry level of <80%	54/236 (22.9)	68/268 (25.4)	0.52
Serious adverse events after intubation — no. (%)			
Septic shock	50 (9.0)	60 (10.8)	0.31
Ventilator-associated pneumonia	95 (17.1)	104 (18.8)	0.46
Cause of death			
Death at day 90 — no./total no. (%)			0.11
Cardiac arrest in ICU	5/98 (5.1)	12/104 (11.5)	
Refractory hypoxemia in ICU	21/98 (21.4)	13/104 (12.5)	
Refractory shock in ICU	11/98 (11.2)	7/104 (6.7)	
Withdrawal of life-sustaining therapy	38/98 (38.8)	38/104 (36.5)	
Death after ICU discharge	23/98 (23.5)	34/104 (32.7)	

* Severe arterial hypotension was defined by any systolic arterial pressure of less than 65 mm Hg or a pressure of less than 90 mm Hg for more than 30 minutes.

partially offset by a higher, albeit generally low, discontinuation rate owing to patients' discomfort. Beyond these patient-centered outcomes, widespread use of high-flow oxygen may also decrease ICU resources associated with the use of invasive mechanical ventilation (i.e., the use of sedatives and invasive ventilation equipment). However, the adoption of this method is limited by substantial resource requirements, such as a supply of high-volume oxygen and a specialized delivery system, factors that pose substantial feasibility challenges, particularly in low- and middle-income countries.

This trial compared oxygenation strategies in a large population of critically ill patients with acute hypoxemic respiratory failure, the majority of whom met the global definition of acute respiratory distress syndrome, thereby enhancing the generalizability of the findings.[29] The other strengths include a well-defined trial protocol with prespecified intubation criteria and a particularly low frequency of crossover treatment. A potential limitation is the absence of a data and safety monitoring board. The trial was classified as low-risk interventional research according to the French regulatory guidelines, a decision that was justified by the minimal risk associated with the interventions because both oxygen strategies are routinely used in the ICU. The high percentage of patients with viral pneumonia could be another limitation of the trial, especially in the context of the Covid-19 pandemic. However, viral pathogens are a common cause of pneumonia, accounting for up to 60% of isolated pathogens.[30] Although data that were collected at the time of intubation suggest that protocol-specified criteria were similar in the high-flow-oxygen and standard-oxygen groups, data were not prospectively collected to assess adherence among the patients who were not intubated. Future studies may evaluate alternative respiratory-support strategies, including personalized noninvasive approaches, with high-flow-oxygen therapy as the control.

The use of high-flow oxygen in patients with acute hypoxemic respiratory failure did not result in significantly lower mortality at day 28 than standard-oxygen therapy.

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